REMARKS

Claims 1-34 are pending. Claim 7 is canceled herein. Claim 9 is amended herein to more clearly set forth aspects of the invention. New claims 35-48 are presented herein. Accordingly, claim 9 as amended herein, original claims 1-3, previously amended or added claims 4-6, 8, and 10-34, and newly presented claims 35-48 are under consideration.

Support for the amendment to claim 9 is found in original claim 9 (which was incorrectly designated as claim 10) and in paragraphs [0023] and [0024] of the Substitute Specification. No issue of new matter is introduced by this amendment.

Support of new claims 35-48 is found throughout the specification and in the original claims. Specifically, support for new claim 35 is found in original claims 8 (incorrectly designated as claim 9) and 3; support for new claim 36 is found in original claims 8 (incorrectly designated as claim 9) and 4; support for new claim 37 is found in original claim 9 (incorrectly designated as claim 10) and in paragraph [0020] of the Substitute Specification; support for new claim 38 is found in original claim 9 (incorrectly designated as claim 10) and in paragraph [0009] of the Substitute Specification; support for new claim 39 is found in original claim 9 (incorrectly designated as claim 10) and in paragraphs [0022] and [0023] of the Substitute Specification; support for new claims 40 and 42 is found in original claims 1 and 4 and in paragraph [0013] of the Substitute Specification; support for new claims 41 and 43 is found in original claim 7 and in paragraph [0013] of the Substitute Specification; support for new claim 44 is found in original claim 1 and in paragraphs [0012] and [0013] of the Substitute Specification; support for new claims 45 and 46 is found in original claim 1 and in paragraph [0015] of the Substitute Specification; and support for new claims 47 and 48 is found in original claim 1 and in paragraphs [0014] and [0030] of the Substitute Specification. No new matter has been introduced into the application by way of new claims 35-48, and the Examiner is respectfully requested to enter these claims.

Rejection Under 35 U.S.C. § 103

Claims 1-17, 19-25, and 28-31 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bonhomme-Faivre et al. (International Journal of Pharmaceutics, 1996,

Vol. 134:99-104) in view of Parthasarathy et al. (Cancer Letters, 1998, Vol. 134:121-128) and Regazzi et al. (Clinical Pharmacokinetics, 1997, Vol. 32:382-402).

As indicated in the Bonhomme-Faivre et al. reference, it is well recognized that chronic oral administration of all trans retinoic acid (ATRA) results in a gradual fall in peak plasma concentrations and area under the experimental concentration/time curve (AUC) values, and an increase in urinary elimination of its metabolite. It is also understood that ATRA is catabolized by cytochrome P450-like enzymes that are autoinducible and, furthermore, that interferon (IFN) depresses the hepatic cytochrome P450 drug metabolizing system and enhances *in vivo* ATRA effects. As detailed therein, the aim of the study was to investigate the influence of IFN on ATRA pharmacokinetics in metastatic renal cancer therapy. It is apparent that the approach of co-administration of IFN with oral ATRA sought to attempt to address the above-indicated limitations regarding chronic use of oral ATRA.

Bonhomme-Faivre et al. repeatedly refer to the results described their paper as **preliminary**. The preliminary nature of their results is further underscored by the fact that their study included a total of only eight patients, of which only six were evaluated at both day 1 and day 90. Indeed, the authors conclude the paper by positing that

> "*If interferon allows plasma ATRA levels to be maintained or increased during chronic ATRA treatment, it would be interesting to determine the interferon dosing schedule (daily?) and dose in order to confirm our results and optimize clinical efficacy.*" See page 103, left column, last paragraph.

It is apparent from the above statement that Bonhomme-Faivre et al. are reserved with regard to any conclusions that can be drawn from the data presented in this admittedly preliminary study. The authors also state that their results appear to conflict with those of Smith et al., and offer that perhaps different dosing levels of IFN can be conjured to explain the disparate results obtained. See page 103, left column, fourth full paragraph. In view of the scientifically well-founded reservations expressed by Bonhomme-Faivre et al. in this reference, and the dissension evident in the field, one of skill in the art would certainly not view this reference as a definitive reference supportive of the efficacious potential of combination oral retinoid/IFN therapy. Thus, this reference fails to present convincing arguments pertaining to the utility of therapeutic regimens directed to a combination of an oral retinoid and an IFN.

Moreover, Applicant notes and concurs with the Examiner's statement that there is no teaching of intravenous administration of ATRA associated with lipid carrier particles in the Bonhomme-Faivre et al. reference. Applicant further offers that there is no suggestion pertaining to administration of **any** retinoid associated with lipid carrier particles in this reference. In view of the above, Applicant asserts that this reference fails to teach or suggest aspects of the presently claimed invention, namely that a combination of a therapeutically effective amount of at least one interferon and a retinoid associated with lipid carrier particles is useful in a method for inhibiting the growth of cancer cells.

Parthasarathy et al. (1998) investigated whether incorporation of ATRA in liposomes would alter its metabolism by comparing cellular metabolism of liposomal ATRA with free drug. These researchers found that liposomal ATRA was metabolized at a slower rate than free drug in microsomes isolated from rat liver and F9 (embryonic teratocarcinoma) cells. They conclude, therefore, that use of liposomal ATRA could have important clinical implications because encapsulation in liposomes appears to protect ATRA from the catabolic enzymes of target cells, thus exposing the target cells to the active form of the drug for longer periods.

As indicated in the Parthasarathy et al. (1998) reference, it is appreciated that long-term oral treatment with ATRA in acute promyelocytic leukemia (APL) patients is associated with a progressive decrease in plasma drug concentration that generally leads to eventual relapse of the disease and retinoid resistance. As stated therein, accelerated clearance of ATRA from plasma is associated with increased drug catabolism and the decline in plasma drug levels may result, in part, from the action of inducible cytochrome P-450 oxidative enzymes which can catabolize ATRA. This reference elaborates that that encapsulation of retinoids in lipid vesicles has been shown to decrease their toxic effects, sequester them at target locations and amplify their therapeutic effect; and cites previous studies in which liposomal ATRA demonstrated reduced in vitro toxicity while retaining full biological activity.

Of particular note, the discussion states that "liposomal incorporation of ATRA could circumvent the two main problems encountered with oral administration of retinoic acid in therapeutic regimens" (emphasis added). See page 125, right column, second full paragraph. The two main problems to which the authors refer are the decline in plasma drug concentration and toxicity. In that Parthasarathy et al. use liposomal ATRA to address the same major problem (namely reduced efficacy of oral retinoids administered

over time) as that for which a combination of an oral retinoid and an IFN was developed, there is no motivation for a skilled practitioner to combine the use of liposomal ATRA with administration of an IFN. In brief, the art presents treatment with liposomal ATRA as an alternative solution to the same problem that is addressed by treatment with a retinoid in combination with an IFN.

Applicant, therefore, asserts that the Parthasarathy et al. (1998) reference teaches away from the present invention because it is directed to administration of L-ATRA, which is recognized in the art as an **alternative** solution to that of combination oral retinoid/IFN therapy, both of which address the problems encountered with prolonged use of oral retinoids. Moreover, Parthasarathy et al. (1998) does not teach or suggest a combination therapy using a retinoid associated with lipid carrier particles and an IFN.

The Regazzi et al. reference is a review article that focuses on the clinical pharmacokinetics of ATRA. As indicated therein, it is appreciated that the biological efficacy of ATRA is impaired by an induced hypercatabolism of the drug leading to reduced sensitivity and resistance. The Regazzi et al. reference teaches that strategies to overcome ATRA resistance include: 1) co-administration of pharmacological inhibitors of cytochrome P450 (CYP) oxidative enzymes; 2) different dosages of the drug; 3) intermittent dose administration; 4) combination of tretinoin with IFNα; and 5) intravenous administration of liposome encapsulated tretinoin.

Regazzi et al. suggest that specific interest pertaining to the combination of tretinoin and IFNα is directed to: 1) possible additive antiproliferative and differentiative effects of the two drugs; and 2) the effect of interferons in limiting intracellular tretinoin oxidation by downregulating the CYP enzymatic system.

Regazzi et al. also teach that liposome encapsulated tretinoin (liposomal tretinoin) was developed to obtain a formulation which can be administered intravenously to provide potential pharmacological advantages over the oral formulation. Potential advantages of using liposomal tretinoin include: 1) reduced clearance of the tretinoin as compared to that observed in subjects administered oral tretinoin; 2) increased biological activity through specific targeting; and 3) decreased toxicity because of altered pharmacokinetics. The authors also offer that liposomal tretinoin would be "probably impractical for extended therapy because of the need for intravenous administration...".

Thus, Applicant asserts that this reference teaches away from the presently claimed invention since Regazzi et al. consider liposomal tretinoin, an aspect of the present invention, impractical for extended therapy.

In that the Regazzi et al. reference clearly offers 1) the combination of tretinoin and IFNα and 2) intravenous administration of liposomal tretinoin as **alternative** approaches, Applicant asserts that there is no teaching or suggestion in this reference that would motivate a skilled practitioner to combine the two approaches to arrive at the claimed invention.

In conclusion, Applicant asserts that there is no teaching or suggestion in any of the above-mentioned references, when considered either alone or in combination, that can reasonably be interpreted to motivate one skilled in the art to treat a subject with a combination of a retinoid associated with lipid carrier particles and an IFN. The art presents these as alternative solutions, each of which is designed to address the same problem, namely the limitations observed with chronic use of oral ATRA (tretinoin). Applicant, therefore, asserts that the Examiner is interpreting these references in light of the present invention and, as such, is using hindsight reconstruction to divine the present invention from the prior art. In view of the above, applicants contend that the rejection of claims 1-17, 19-25, and 28-31 under 35 U.S.C. §103(a) is improper and respectfully request that the rejection be withdrawn.

Claims 1-17, 19-25, and 28-31 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bonhomme-Faivre (International Journal of Pharmaceutics, 1996, Vol. 134:99-104) in view of Parthasarathy et al. (Cancer Letters, 1998, Vol. 134:121-128) and Regazzi et al. (Clinical Pharmacokinetics, 1997, Vol. 32:382-402) and further in view of Lippman et al. (International Journal of Cancer, 1997, Vol. 70:481-483) and Parthasarathy et al. (Cancer Chemother Pharmacol, 1994, Vol. 34:527-534).

Applicant affirms that the arguments presented herein above with regard to the rejection of claims 1-17, 19-25, and 28-31 under 35 U.S.C. §103(a) as allegedly unpatentable over Bonhomme-Faivre in view of Parthasarathy et al. (1988) and Regazzi et al. are equally well applied in the context of this rejection wherein these references are combined with Lippman et al. and Parthasarathy et al. (1994).

The Lippman et al. reference is a review of various clinical studies wherein retinoids were used in conjunction with interferons. The authors state that, with regard to

the studies, "most have focused on refractory solid tumors and achieved negative results". The reference does, however, indicate that encouraging results have been observed in three advanced solid tumor types including squamous cell carcinoma, cervix, and renal cell carcinoma. The Lippman et al. reference does not teach or suggest administration of a retinoid associated with lipid carrier particles. Moreover, this reference fails to teach or suggest treating a subject with a combination of a retinoid associated with lipid carrier particles and an IFN. This reference, therefore, fails to remedy the deficiencies of any one of Bonhomme-Faivre, Parthasarathy et al. (1988) or Regazzi et al., or a combination thereof.

The Parthasarathy et al. (1994) reference describes experiments that investigated the effects of liposomal ATRA on a squamous cell carcinoma line and its multicellular tumor spheroid (MTS) model. The introduction teaches that liposomal encapsulation is known to decrease retinoid toxicity, sequester retinoids from rapid metabolism, amplify the therapeutic effect of retinoids, and improve the solubility of lipophilic drugs such as retinoids. The authors observed that liposomes can serve as an effective carrier system for delivery of retinoids to squamous cell carcinomas. Moreover, they found that liposomal retinoids exhibit growth inhibitory effects comparable to those of the free drug. Notably, there is no suggestion in the Parthasarathy et al. (1994) reference to combine a therapeutic regimen involving liposomal retinoids with a protocol directed to IFN administration. Thus, this reference fails to remedy the deficiencies of any one of Bonhomme-Faivre, Parthasarathy et al. (1988) or Regazzi et al., or a combination thereof.

In summary, neither the Lippman et al. reference nor the Parthasarathy et al. (1994) reference, or a combination thereof, remedy the defects of Bonhomme-Faivre, Parthasarathy et al. (1988) or Regazzi et al., when viewed in isolation or in combination.

In view of the above, applicant asserts that the rejection of claims 1-17, 19-25, and 28-31 under 35 U.S.C. §103(a) as allegedly unpatentable over Bonhomme-Faivre in view of Parthasarathy et al. (1994) and Regazzi et al. and further in view of Lippman et al. and Parthasarathy et al. (1994) is without merit and respectfully requests that the rejection be withdrawn.

Claims 1-17, 19-25, and 28-31 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bonhomme-Faivre (International Journal of Pharmaceutics, 1996, Vol. 134:99-104) in view of Parthasarathy et al. (Cancer Letters, 1998, Vol. 134:121-128) and

Regazzi et al. (Clinical Pharmacokinetics, 1997, Vol. 32:382-402) and further in view of Marth et al. (Journal of the National Cancer Institute, 1986, Vol. 77:1197-1202) and Parthasarathy et al. (Cancer Chemother Pharmacol, 1994, Vol. 34:527-534).

Applicant reaffirms that the arguments presented herein above with regard to the rejection of claims 1-17, 19-25, and 28-31 under 35 U.S.C. §103(a) as allegedly unpatentable over Bonhomme-Faivre in view of Parthasarathy et al. (1998) and Regazzi et al., or in further view of Lippman et al. and Parthasarathy et al. (1994), are equally well applied in the context of this rejection wherein Bonhomme-Faivre, Parthasarathy et al. (1998), and Regazzi et al. are combined with Marth et al. and Parthasarathy et al. (1994).

The Marth et al. reference describes in vitro experiments that investigated synergistic interactions between ATRA and interferons in the treatment of human mammary carcinoma cell lines and a human lung and laryngeal carcinoma cell line. The results revealed that the effect of combination therapy using ATRA and interferons varied among the different cell lines examined. Synergistic action was most pronounced when ATRA was used in combination with IFNγ. The Marth et al. reference is silent with regard to the use of liposomal ATRA in any context. Thus, this reference fails to remedy the deficiencies of any one of Bonhomme-Faivre, Parthasarathy et al. (1988) or Regazzi et al., or a combination thereof.

As discussed herein above, the Parthasarathy et al. (1994) reference offers no teaching directed to combining a therapeutic regimen involving liposomal retinoids with a protocol directed to IFN administration. Thus, this reference fails to remedy the deficiencies of any one of Bonhomme-Faivre, Parthasarathy et al. (1988) or Regazzi et al., or a combination thereof.

In summary, neither the Marth et al. reference nor the Parthasarathy et al. (1994) reference, or a combination thereof, remedy the defects of Bonhomme-Faivre, Parthasarathy et al. (1988) or Regazzi et al., when examined in isolation or in combination.

In view of the above, applicant asserts that the rejection of claims 1-17, 19-25, and 28-31 under 35 U.S.C. §103(a) as allegedly unpatentable over Bonhomme-Faivre in view of Parthasarathy et al. (1994) and Regazzi et al. and further in view of Marth et al. and Parthasarathy et al. (1994). is inappropriate and respectfully request that the rejection be withdrawn.

Objections

Applicant notes that claims 8, 27, and 32-34 are objected to for being dependent on rejected base claims. In view of the above arguments, applicant anticipates that these claims and the other pending claims are now in condition for allowance.

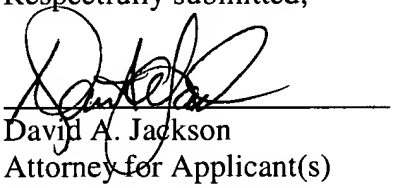
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



David A. Jackson
Attorney for Applicant(s)
Registration No. 26,742

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, New Jersey 07601
(201) 487-5800
August 10, 2004

Enclosures: Petition for a Three-Month Extension of Time